Investigator Responsibilities – Regulation and Clinical Trials

FDA'S 2012 Clinical Investigator Training Course

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Objectives

- Identify the federal regulations covering clinical research and clinical investigator obligations
- Discuss specific problems seen during FDA inspections at clinical sites
- Discuss various methods that can be used to ensure compliance with federal regulations and study protocol requirements

Who is an Investigator?

- An individual who actually conducts a study (i.e. under whose immediate direction the drug is dispensed to a subject.)
- In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

  [21 CFR 312.3]

Sponsor-Investigator

- An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
  - The term does not include any person other than an individual.
  - The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

[21 CFR 312.3]

Question ?

- *Does the investigator have to be a medical doctor?*

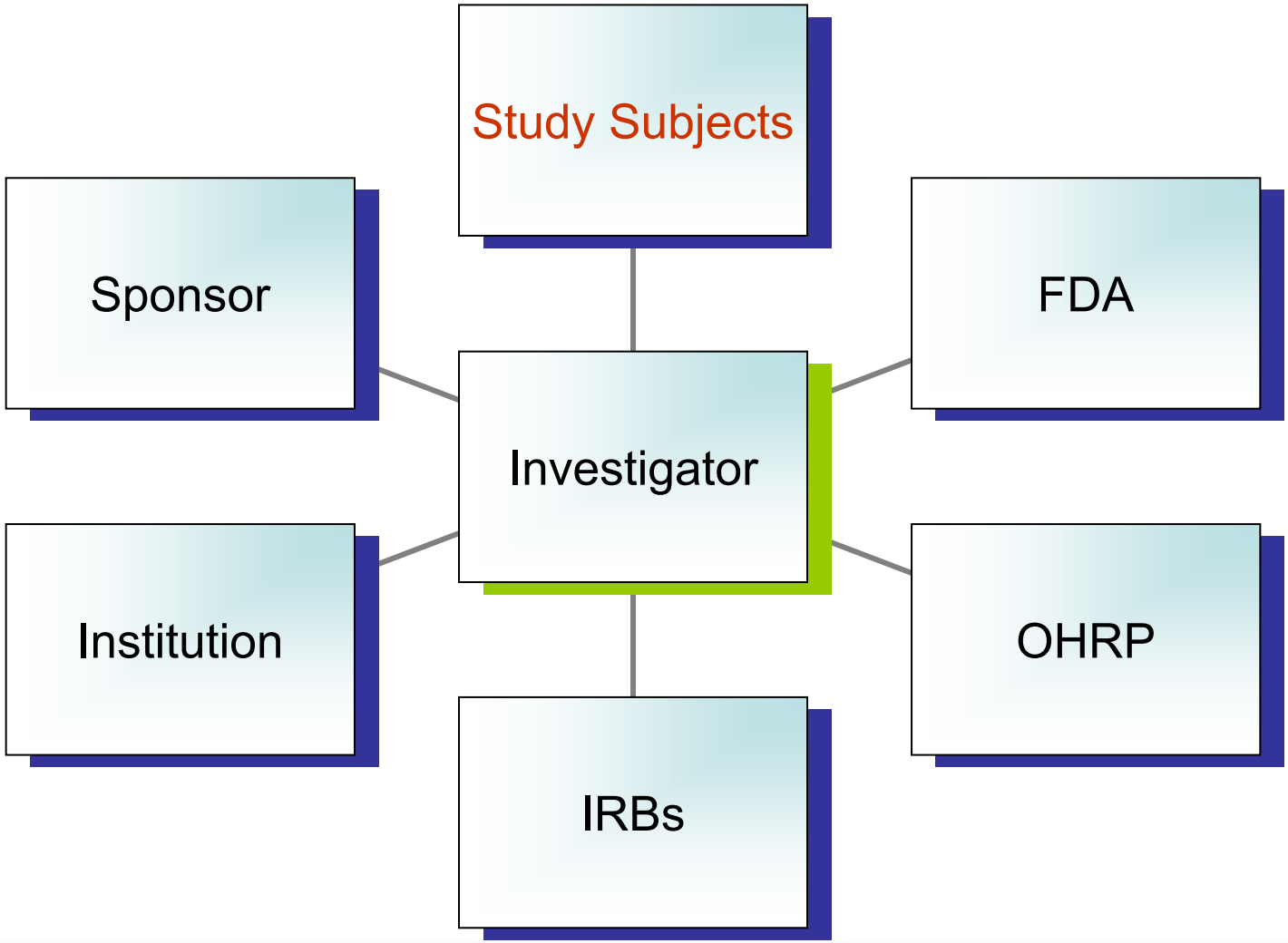
ANSWER: **NO A physician can be a subinvestigator to perform those study functions requiring the appropriate level of medical expertise.**

[21 CFR 312.53(a)]

Legal Framework

- Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - Section 505(i) is the statutory authority for FDA's oversight of clinical investigations to test safety and effectiveness
- Code of Federal Regulations (CFR)
  - Regulations promulgated under Section 505(i) describing FDA's authority over the conduct of clinical investigations including
    - Sponsor responsibilities
    - Clinical Investigator responsibilities
- Guidances
  - Advisory only, to assist clinical investigators and sponsors in complying with the regulations

Clinical Trial Environment



FDA Expectations of Clinical Investigators

- Adherence to Code of Federal Regulations
  - Knowledge of Clinical Investigator regulations
  - Understanding of Clinical Investigator responsibilities

National Archives and Records Administration

code of federal regulations

Statement of Investigator Form FDA 1572

No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572

[21 CFR 312.53(c)].

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c))

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

CURRICULUM VITAE OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:
FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.
☑ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:
I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
I agree to personally conduct or supervise the described investigation(s).
I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:
1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number".

Please **DO NOT RETURN** this application to this address.

Commitments on 1572

- Personally conduct or supervise investigation
- Follow protocol- only make changes after notifying the sponsor unless subject at risk
- Ensure all persons assisting with the study are informed of obligations
- Inform subjects that drugs are being used for investigational purposes
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64)

Commitments (cont.)

- Maintain adequate and accurate records (21 CFR 312.62) and make them available for inspection in accordance with 21 CFR 312.68
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards
- Comply with other requirements in 21 CFR 312

Form FDA 1572

- If a clinical study is conducted outside of the U.S. and is not conducted under an IND, then the investigator need not sign a 1572
- If a foreign clinical study is conducted under an IND, then all FDA IND regulations, including the requirement to obtain a signed 1572, must be met
- If local laws or regulations prohibit the signing of a 1572, FDA would expect the sites to operate as non-IND sites

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs

Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

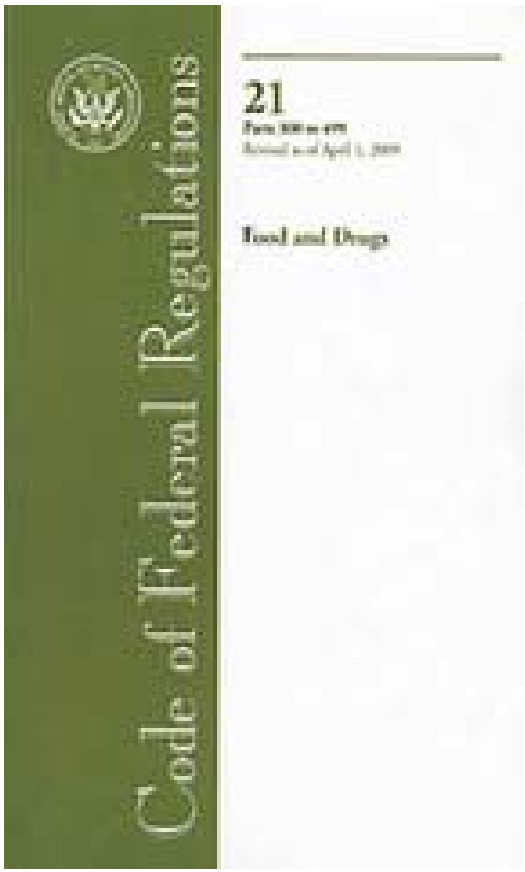
May 2010
Procedural

E6: Good Clinical Practice: Consolidated Guideline

- Published as official guidance in U.S. Federal Register (**May 1997**)
  - "The objective of this ICH GCP guidance is to provide a **unified standard** for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions".

In General…E6 More Detailed

- Differences can especially be seen in the area of Sponsor responsibilities
  - ICH E6 more detailed for monitoring and QA
- However, FDA regulations are more explicit in the IRB sections



Question?

- Do FDA regulations allow for delegation of the informed consent?

Answer: Not really but…

- FDA has no regulations concerning delegation of this duty
  - Discussed in the FDA Information Sheets: "*FDA does not require the investigator to personally conduct the consent interview.*"

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm

- ICH allows the delegation of the informed consent process to a designee
  - "The investigator, or a person designated by the investigator, should fully inform the subject…"

Question ?

- Does the investigator have to sign the informed consent?

ANSWER: **NO** Signing/dating by person conducting the informed consent discussion is part of ICH-GCP but not FDA regulations

Role of Clinical Investigators

- Good Clinical Practice (GCP) in FDA-regulated research is not the same as good clinical practice in caring for patients
  - For example, FDA regulations have very specific requirements for following the protocol, recordkeeping, and drug accountability

Important Caveat for Clinical Investigators

Standards for clinical care of patients

≠

Standards for academic research

≠

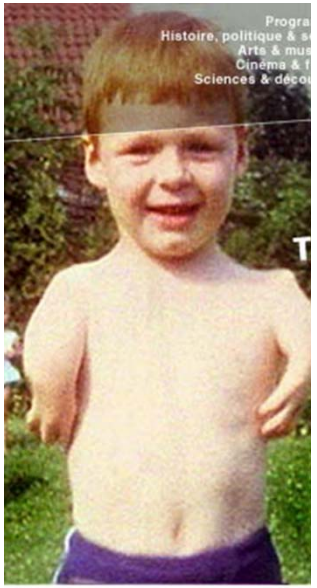
Standards for FDA regulated research

Historical Perspective

- ***1961-1962: Thalidomide tragedy***

  Exposed loopholes in Food, Drug and Cosmetic Act of 1938: Companies could distribute unapproved drugs for experimental purposes

  - Did not require notification to patients of investigational status
  - Did not require companies or doctors to keep track of distribution
  - Did not require FDA to be notified of experimental use
  - Did not require records to be kept
  - Did not require demonstration of drug effectiveness



Action

- ***1962: Kefauver-Harris Amendments***
  - Approval based on demonstration of efficacy as well as safety
  - Expanded inspectional authority - FDA can inspect company records regarding development and clinical testing
  - FDA must be notified before clinical trials could be conducted
  - Rulemaking authority over “Investigational New Drugs”
  - Expansive rulemaking authority over clinical trials
  - Gave FDA the power to halt clinical trials

Additional Actions

- ***IND Regulations of 1963***
  - Created the current framework of clinical trials
  - Investigations must be “adequate” and “well-controlled”
  - Investigators qualified by scientific training and experience
  - Recordkeeping requirements
  - Informed Consent

Who's in Charge at the Study Site?

- Clinical investigators are in charge ***and*** held accountable
  - FDA regulations permit sponsors to delegate their responsibilities to Contract Research Organizations (CROs) but do ***not*** permit clinical investigators to delegate their general responsibilities to CROs or site management organizations, subinvestigators, or study staff
- Penalties for significant noncompliance
  - Warning Letters (posted on FDA website)
  - Disqualifications/Restrictions/Debarments (posted on FDA website)
  - Criminal prosecutions/prison/fines

General Clinical Investigator Responsibilities [21 CFR 312.60]

- Ensuring that an investigation is conducted according to the
  - Signed investigator statement (Form 1572)
  - Investigational plan
  - Applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Control of drugs under investigation
- Ensuring that informed consent is adequately obtained according to 21 CFR 50
- Ensuring IRB review, approval and reporting requirements are met per 21 CFR 56

Investigator Responsibilities

- Control of investigational drug (312.61)
- Record keeping and retention (312.62)
  - An investigator is responsible for:
    - Maintaining adequate records of the disposition of the drug
    - Accurate case histories that record all observations, and
    - Other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation
  - An investigator is required to maintain investigation records for:
    - 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated
    - 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication

Responsibilities (cont.)

- Investigator reports (312.64)
  - Progress reports to sponsor
  - Safety reports
    - Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
    - Record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol
  - Final report to sponsor
  - Financial disclosure to sponsor
    - Promptly update as needed during the course of the investigation and for 1 year following study completion

ClinicalTrials.gov

- **U.S. Public Law 110-85** (Food and Drug Administration Amendments Act of 2007 or **FDAAA**), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain “applicable clinical trials”
  - Trials of Drugs and Biologics: controlled clinical investigations, other than Phase 1 investigations, subject to FDA regulation
  - Trials of Devices: Controlled trials with heath outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric postmarket surveillance
- FDA requires a statement in the informed consent regarding ClinicalTrials.gov.

  http://clinicaltrials.gov/ct2/manage-recs/fdaaa

Question

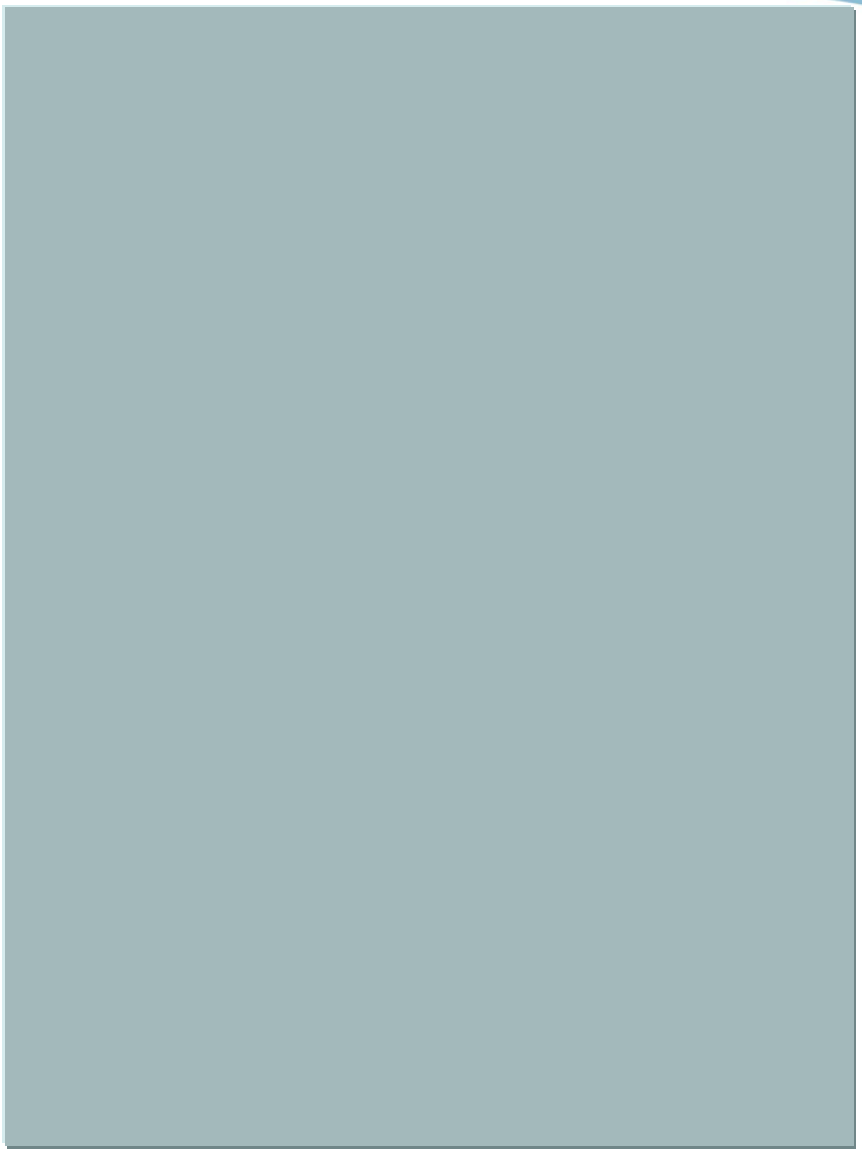
- What documents must be submitted to the IRB for review?

Answer

- FDA: The IRB should receive and review **all research activities**
  - Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects
- FDA Guidance: *The documents reviewed should include the complete documents received from the clinical investigator, such as the protocol, the investigator's brochure, a sample consent document and any advertising intended to be seen or heard by prospective study subjects.*
- ICH specifically requires IRB submission of:
  - informed consent, protocol/amendments, and advertisements
  - Written information provided to subjects
  - Information about subject payment/compensation
  - Investigator's Brochure
  - Investigator's current CV and/or qualifications

Sponsor Responsibilities

- Sponsors are responsible for (312.50):
  - Selecting qualified investigators
  - Providing them with the information they need to conduct the investigation properly
  - Ensuring proper monitoring of the investigation
  - Ensuring that the investigation is conducted in accordance with the general investigational plan
  - Maintaining an effective IND
  - Ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects or risks



Outlines FDA expectations for study oversight

- Delegation of study tasks
- Training of study staff
- Supervision of conduct of ongoing study
- Oversight of third parties involved in the study (e.g. SMOs, outside labs specifically retained to conduct study assessments)

***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf**

Guidance (cont.)

- Outlines FDA expectations for protecting the rights, safety, and welfare of subjects
  - Provision of reasonable medical care for issues related to study participation (e.g. to manage an adverse event)
  - Facilitation of care for other health issues that might arise during the study
  - Avoiding exposure of subjects to unreasonable risks

Question

- Can the investigator delegate the activities around investigational product?

Answer

- FDA has no regulation concerning delegation of these duties
  - The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task (*per FDA Investigator Guidance 2009).*

- ICH allows the delegation of study drug dispensing, patient counselling, and drug accountability to an “appropriate” designee

In Summary

- Follow the current protocol
- Personally conduct or supervise investigation(s)
  - Ensure that all persons assisting in conduct of studies are informed of their obligations
- Ensure informed consent (21 CFR 50) and IRB review, approval , and reporting (21 CFR 56) requirements are met

In Summary (cont.)

- Obtain the informed consent of each human subject to whom the drug is administered
- Notify the sponsor before making changes in the protocol
- Notify the IRB and obtain IRB approval before making changes in the protocol
- Report adverse events to the sponsor

In Summary (cont.)

- Maintain adequate and accurate records
- Make records available for inspection
- Comply with all other requirements in 21 CFR 312
- Report Financial Interests to the Sponsor

DON'T

- Over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- Erase, white-out or obliterate original data entry
- Accept suggested changes to study data without checking the source documents or without justification for such changes
- Backdate the consent forms and signatures
- Forget to obtain IRB approval of consent form revisions
- Revise the protocol without obtaining the sponsor's written concurrence
- Use your staff as subjects in a study not having the condition(s) under investigation
- Destroy study records

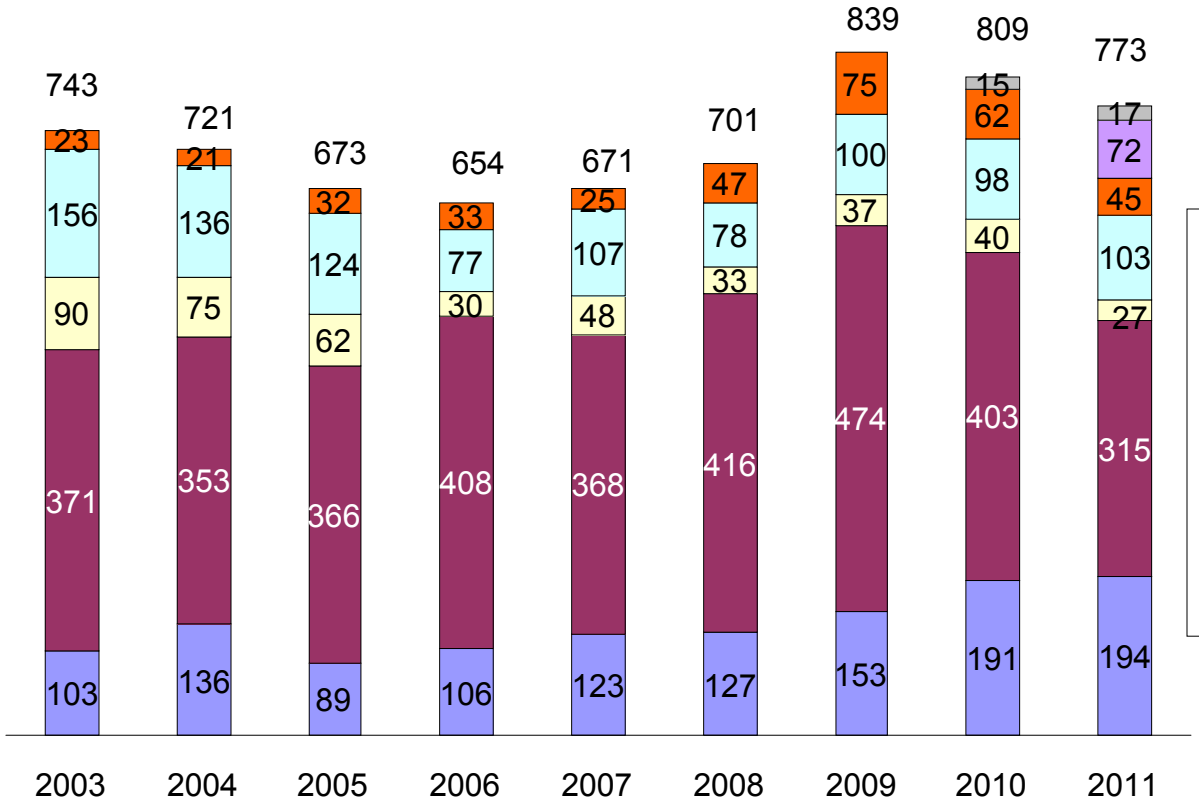
Regulatory Authority to Conduct Inspections/Audits

- Section 505(k)(2) of the Food, Drug, and Cosmetic Act mandates that FDA shall have access to and copy and verify the required clinical study records.
- **21 CFR 312.68**
  - "An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator…"

Typical Questions in an Interview

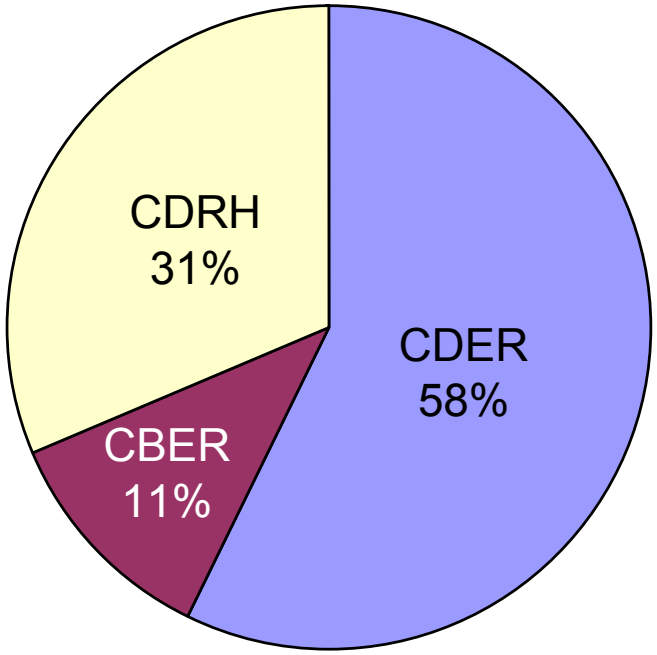
- Delegation of authority: Who, when, where:
  - Screening of subjects
  - Interpreting screening results/admitting to the study
  - Informed Consent of subjects
  - Receipt of test article; handling; administration; return
  - Reporting (including safety reporting) /transcribing data
  - Clinical laboratory
  - Archiving study data

Inspections Overseen by OSI * (CDER, FY 2003 - FY 2011)



- *Based on inspection start date – [OSI database as of January 18, 2012]
- IRB includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH, Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- As of June 2011, Postmarketing Adverse Drug Event and Risk Evaluation and Mitigation Strategy inspection programs were incorporated into OSI

Clinical Investigator Inspections*
(All Centers, FY 2011)

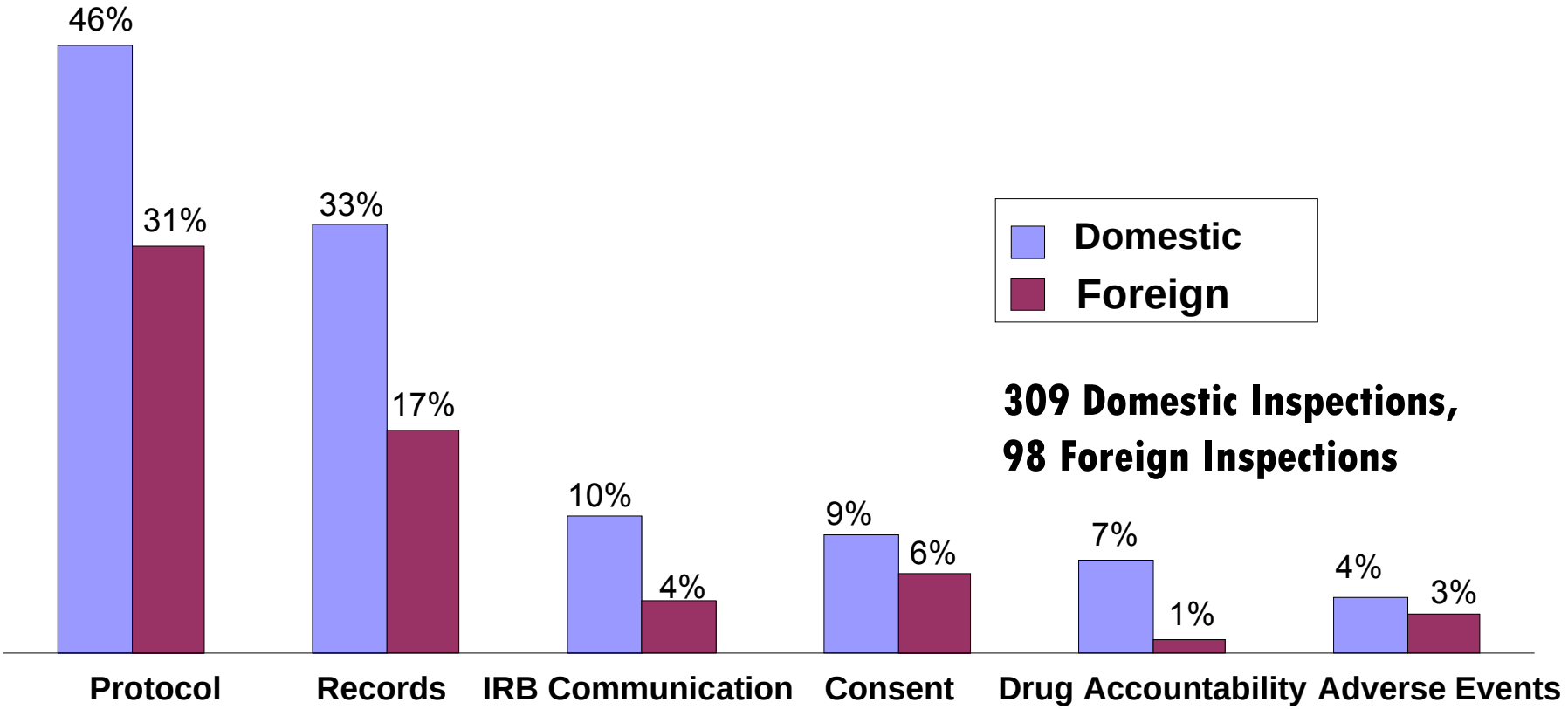


CDER	**=**	**317**
CBER	**=**	**62**
CDRH	**=**	**174**
Total		**553**

CDER = Center for Drug Evaluation and Research, CBER = Center for Biologics Evaluation and Research, CDRH = Center for Devices and Radiological Health

- *CDER numbers based on inspection start date – [OSI database as of July 25, 2012]
- CDRH numbers based on inspection end date
- CBER numbers based on end date of classified inspections

Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection



- *Based on letter issue date; Inspections may have multiple deficiencies, [OSI database as of July 25, 2012]
- Note that this does not denote number of inspections completed in FY 2011, but rather number of inspection reports evaluated and closed in FY2011

Compliance Classifications

NAI - No Action Indicated

Inspected Entity is in compliance

VAI - Voluntary Action Indicated

Minor deviation(s) from the regulations

Voluntary correction is requested

OAI - Official Action Indicated

Serious non-compliance requiring regulatory or administrative action by FDA

Inspectional Outcomes

- No Action Indicated
- Form FDA 483
  - 15 business days to reply

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

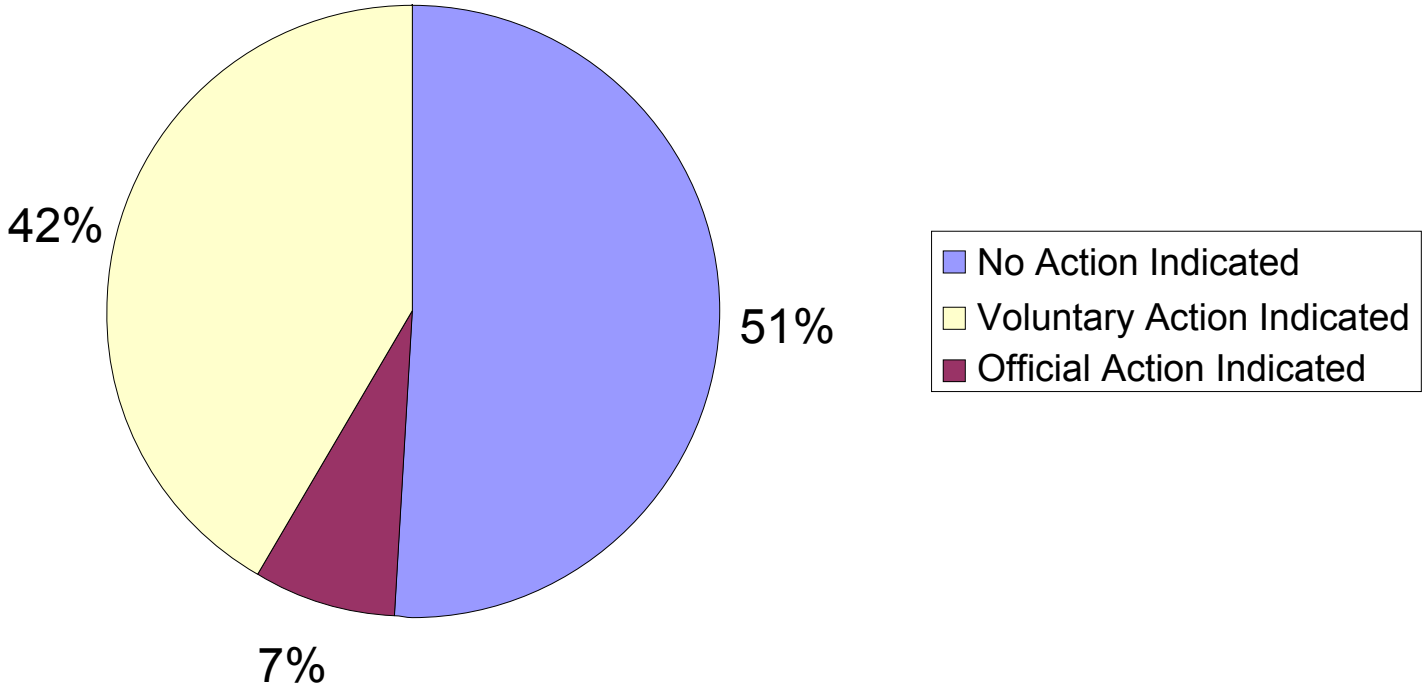
DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED **TO:**	
FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

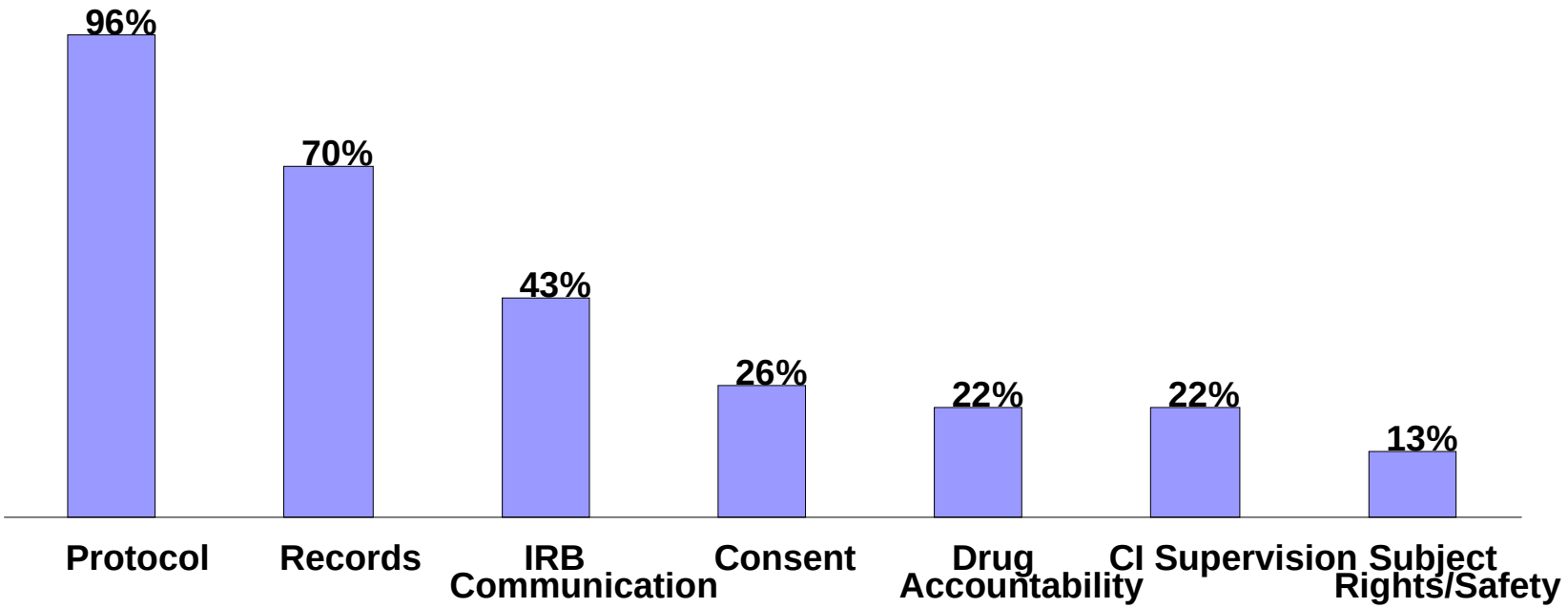
CDER Clinical Investigator Inspections Final Classification* (FY 2011)

(total=312)



***Based on Letter Issue date; Includes OAI Untitled Letters, [OSI database as of July 25, 2012]**

Frequency of Clinical Investigator Related Deficiencies Based on Post-Inspectional Correspondence Issued: OAI* Final Class (CDER, FY2011)**



*OAI: Denotes Official Action Indicated (significant deficiencies found)
**Based on letter issue date [OSI Database as of 1/18/2012]; Inspections may have multiple deficiencies, Includes OAI untitled letters

Reference

- **Inspection Observations**

  Spreadsheets summarizing the areas of regulation cited on FDA's system-generated 483s by fiscal year

  http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm

Reference

- **Inspections Classification Database and Search (Oct. 2008–March 2012)**

  Final inspection classification for inspections related to currently marketed FDA-regulated products. (*Some information may be withheld from posting as to not interfere with enforcement action*).

  http://www.fda.gov/ICECI/EnforcementActions/ucm222557.htm

Common mistakes – Risk factors for non-compliance

- Poor supervision and training of study staff
- Insufficient investigator involvement in study conduct
- Inappropriate delegation of study tasks to unqualified persons
- Failure to adequate protect study subjects
- Overworked investigator and study staff (e.g. too many subjects, complex study with large data collection, too many concurrent studies)

Regulatory Actions

- Warning Letter
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
- Disqualification of clinical investigator
- Criminal Investigation by Office of Criminal Investigations (OCI)
  - Debarment

Reference

- List of Warning Letters

  http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

- Regulatory Procedures Manual Section on Warning Letters

  http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

Investigator Disqualification

- 21 CFR 312.70
  - Repeated and deliberate failure to comply with the requirements
  - FDA provides notice of matter to investigator and provides opportunity to explain (informal hearing)
  - Opportunity for formal hearing
  - May result in ineligibility to receive investigational drugs

Reference

- **Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)**

  FDA believes it has evidence that the clinical investigator repeatedly or deliberately violated FDA's regulations governing the proper conduct of clinical studies involving investigational products or submitted false information to the sponsor and is initiating an administrative proceeding to determine whether the clinical investigator should be disqualified from receiving investigational products.

  http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm092185.htm

Example

- I. Submission of false information. The Center has received affidavits that indicate you submitted false information to the sponsor in a required report [21 CFR 312.70].
  - A. You report that subject #7206 was enrolled in the pediatric study and completed all four required visits, but the subject's mother states that this subject did not have an ear infection, and did not participate in the study.
  - B. You report that subject #7223 was enrolled in the pediatric study and completed all four required visits, but the subject's mother states that this subject did not have an ear infection, and did not participate in the study.

Reference

- **Disqualified/Restricted/ Restrictions Removed/ Assurance Lists for Clinical Investigators**

  Restricted from receiving investigational drugs, biologics, or devices if FDA determines that the investigator has repeatedly or deliberately failed to comply with regulatory requirements for studies or has submitted false information to the study's sponsor.

  http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm

Reference

- **FDA Debarment List (Drug Product Applications)**

  Firms or individuals convicted of a felony under Federal law for conduct (by a firm) relating to the development or approval of any drug product or abbreviated drug application

http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm2005408.htm

Case Study
Data Validation Inspection for New Drug Application (NDA)

- Failure to prepare and maintain adequate case histories and retain records [21 CFR 312.62(b) and (c)]
  - eCRFs were source documents; Site data for inspection consisted of CD provided by sponsor, no evidence that CI prepared or maintained subject records or signed off on subject data in real time
  - Clinical signs such as breath sounds and chest exam were assessed during phone call to subjects
  - Data in eCRF inaccurately carried over from visit to visit

The New York Times

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SUNDAY, FEBRUARY 6, 2005

Abuses Endangered Veterans In Cancer Drug Experiments

By DEBORAH SONTAG

ALBANY — Carl M. Steubing, a decorated Battle of the Bulge veteran whose experience of war made him a pacifist but also instilled in him a zest for living life at full tilt, took his diagnosis of gastroesophageal cancer in 2001 as a challenge.

With a thatch of white hair and a rich baritone voice, Mr. Steubing, at 78, was not ready to succumb to illness. A retired music educator and wedding photographer, he remained active as a church choir director, expert cook, painter, golfer and fisherman. He was married to a woman 24 years his junior, and they had seven children and three grandchildren between them.

Mr. Steubing jumped at the chance to participate in an experimental drug study at the Stratton Veterans Affairs Medical Center in Albany, believing it offered him the hope of surviving longer. The research coordinator, Paul H. Kornak, told Mr. Steubing that he was "just a perfect specimen," with the body of a man half his age, according to Jayne Steubing, Mr. Steubing's widow.

He was not, though. Because of a previous cancer and poor kidney function, Mr. Steubing was not even eligible to participate in the experiment, according to government documents. Mr. Kornak, however, brushed that obstacle aside. He altered Mr. Steubing's medical records, according to prosecutors, and enrolled him in the study. He also posed as a doctor.

Paul H. Kornak, who posed as a doctor for veterans, in 1999.

IN HARM'S WAY
Research, Fraud and the V.A.

In 2001, Mr. Steubing endured about six periodic treatments with an aggressive three-drug chemotherapy combination. Each infusion made him violently ill and forced his hospitalization. He died in March 2002.

Last month, at the federal courthouse in Albany, Mrs. Steubing glared at Mr. Kornak, 53, as he pleaded guilty to fraud, making false statements and criminally negligent homicide in the death of an Air Force veteran, James DiGeorgio. When Mr. Kornak admitted to falsifying the medical data of "subject initials CMS" — Carl M. Steubing — Mrs. Steubing's face crumpled.

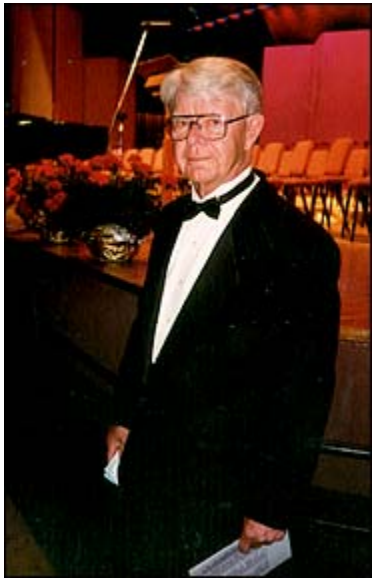
Mr. Kornak, who is scheduled to be sentenced in May, also agreed to cooperate in a widening investigation of the hospital's cancer research program. From 1999 to 2003, when he worked there, scores of veterans were, at the least, put at risk. But allegations of carelessness, fraud and patient abuse in the hospital's cancer research program predated Mr. Kornak, and employees say that administrators not only dismissed their concerns, but harassed them for standing up for the veterans.

"Research violations were a way of life at Stratton for 10 years," said Jeffrey Fudin, a pharmacist at the hospital. "Stratton officials turned a blind eye to unethical cancer research practices and punished those who spoke out against them. The whole Kornak episode could have been prevented."

According to Mr. Kornak's lawyer, E. Stewart Jones, there was a "clear systems failure," permitting a research culture where "rules weren't followed, protocols weren't applied and supervision was nonexistent."

It was also a culture whose de-

Continued on Page 18



In September, however, the Food and Drug Administration started proceedings to disqualify Dr. Holland from conducting further clinical research because he had "failed to protect" subjects under his care in Albany.

According to the F.D.A., patients' medical records were altered in at least five experimental drug studies, enabling veterans like Mr. Steubing to be enrolled in studies for which they were either too sick or too healthy to qualify. A patient with coronary disease, for instance, was enrolled in a study that excluded heart patients because of a risk of hemorrhages. A patient with impaired renal function was administered a drug toxic to kidneys that probably contributed to his death, the agency said.

Routine Visit Leads to an Inquiry

In December 2001, a clinical research associate for Ilex Oncology made a routine visit to the Albany veterans' hospital, where Ilex was sponsoring a bladder cancer study.

Ilex, a cancer drug company, was offering the Albany research program $2,500 for each study subject. Such payments are a standard practice, and many researchers say that they barely cover the cost of conducting the studies. Critics of drug-testing practices, however, consider the payments a threat to scientific integrity.

Ilex's research associate discovered some paperwork that raised suspicions, according to Caren Arnstein, a spokeswoman for the Genzyme Corporation, which bought Ilex at the end of last year.

"Things about the dates didn't look right," Ms. Arnstein said. "If the results of a pathology report for a biopsy are dated prior to the biopsy being taken — something seemed off."

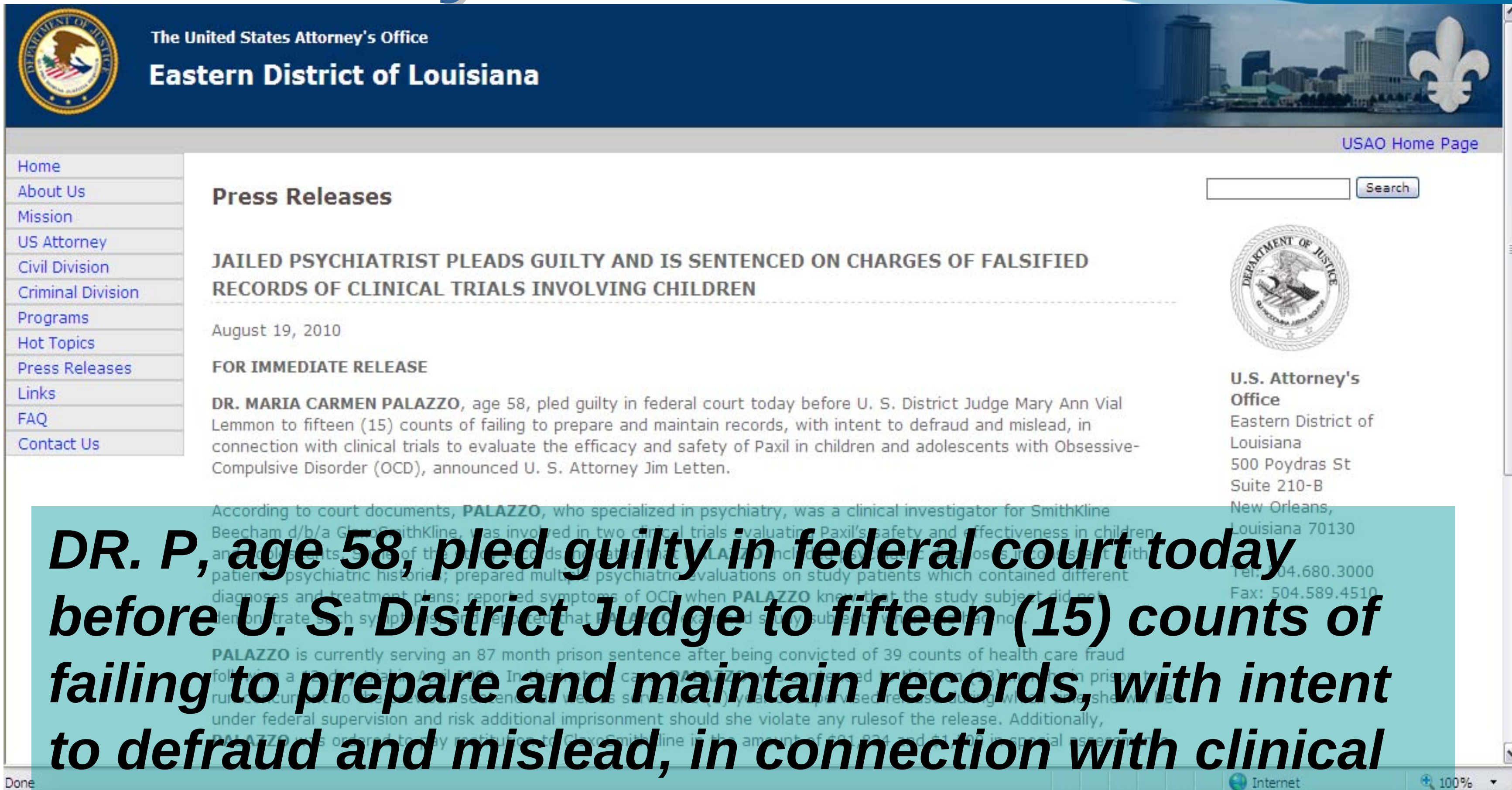
The discrepancies led to an audit by Ilex. In the spring of 2002, the Albany hospital began an internal review of the cancer research program, eventually referring the matter to the inspector general, according to The Times Union.

Ilex shut down the Albany study and alerted the F.D.A. The agency had also received another complaint, an F.D.A. official said.

Case Study: Lax Supervision

- Study coordinator enrolled ineligible subjects in oncology trials
- Coordinator altered source records and created fraudulent CRFs to make subjects appear eligible
- Data manipulations should have been apparent to attentive clinician
- Subject who was ineligible due to poor renal and liver function was enrolled, dosed, and died as a result
- Study coordinator sentence to 71 months in prison and debarred from any future involvement in FDA regulated research
- Dr. Holland – 5 years probation, $500k restitution to defrauded drug companies, disqualified

Case Study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JAILED PSYCHIATRIST PLEADS GUILTY AND IS SENTENCED ON CHARGES OF FALSIFIED RECORDS OF CLINICAL TRIALS INVOLVING CHILDREN

August 19, 2010

FOR IMMEDIATE RELEASE

DR. MARIA CARMEN PALAZZO, age 58, pled guilty in federal court today before U. S. District Judge Mary Ann Vial Lemmon to fifteen (15) counts of failing to prepare and maintain records, with intent to defraud and mislead, in connection with clinical trials to evaluate the efficacy and safety of Paxil in children and adolescents with Obsessive-Compulsive Disorder (OCD), announced U. S. Attorney Jim Letten.

According to court documents, **PALAZZO**, who specialized in psychiatry, was a clinical investigator for SmithKline Beecham d/b/a GlaxoSmithKline, was involved in two clinical trials evaluating Paxil's safety and effectiveness in children ...

PALAZZO is currently serving an 87 month prison sentence after being convicted of 39 counts of health care fraud ...

under federal supervision and risk additional imprisonment should she violate any rulesof the release. Additionally, ...

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Done
Internet
100%

DR. P, age 58, pled guilty in federal court today before U. S. District Judge to fifteen (15) counts of failing to prepare and maintain records, with intent to defraud and mislead, in connection with clinical trials to evaluate the efficacy and safety of Paxil in children and adolescents with Obsessive-Compulsive Disorder (OCD)…

How can clinical investigators ensure high quality data and subject safety?

- **Select qualified staff and ensure adequate training and supervision**
  - Ensure staff are not performing tasks they are not qualified to do (e.g. assessing eligibility, performing physical exams, assessing adverse events)
  - Ensure oversight of sub-investigators and study staff

Improve Process — Be Proactive

- **Address human factors in systems**
  - Hire experienced, qualified staff
  - Avoid conflicts of interest/financial incentives
  - Decrease number of times data are handled
  - Assess ability to comply with protocol visits; laboratory testing; electronic systems for data capture, archiving and transmission to sponsor; maintaining records, drug accountability, inspections by FDA

Improve Process — Be Proactive

- **Create systems that limit opportunity for errors**
  - Simplify protocol and outcomes assessed
  - Be realistic about the amount of data to be collected
  - Standardize systems and formats where possible
  - Use validated instruments/definitions
  - Write down all procedures (SOPs). Use checklists.
  - Don’t re-invent the wheel
  - Keep amendments to a minimum and check the CRFs and consent form against each change

Improve Process

- **Develop an integrated framework**
  - Data and Safety Monitoring Plan, Data Management Plan, Quality Assurance Plan, Data Analysis Plan
  - Insist on training and then test it
  - Think very carefully about unblinding procedures
  - Have a disaster plan (for staff turnover, floods, etc.)
  - Do beta-testing/dry-runs
  - Have weekly team meetings/calls
  - Audit yourself — be open and honest

Implement System to Detect and Correct Errors in Real Time

- Do real-time cleaning of the data
- Pay attention to monitoring queries and respond promptly ***Close loops***
- Audit trail of changes should make clear what was changed, who changed it, and why it was changed
- Evaluate need for system wide corrections and training

Key Messages

- Clinical investigators play a critical role in ensuring high quality studies
- Good care of patients is not the same as Good Clinical Practices (GCP) in research
  - Ensure that all staff have a clear understanding of responsibilities under FDA regulations
- At stake is public confidence and participation in the clinical trials and ultimately the availability of safe and effective products

The "cost of quality" isn't the price of creating a quality product or service. It's the cost of NOT creating a quality product or service.

*Principles of Quality Costs: Principles, Implementation, and Use, Third Edition, ed. Jack Campanella

FDA Sites of Interest

- Running Clinical Trials

  http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

- FDA Basics for Industry

  http://www.fda.gov/ForIndustry/FDABasicsforIndustry/default.htm

- Sign up for Updates

  http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234630.htm

FDA Sites of Interest

- Replies to Inquiries to FDA on Good Clinical Practice
  - Designed to simplify the search for copies of e-mail messages (including the original inquiry and associated reply(ies)) that have been submitted by the public to the Good Clinical Practice Program's gcp.questions@fda.hhs.gov e-mail account.

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm

Guidances of Interest

- **FDA Inspections of Clinical Investigators-Information sheet**

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf

- **Guidance for Industry-Investigator Responsibilities**

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Thank you for your attention